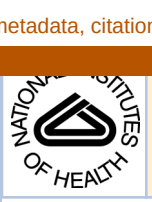

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Assessing the effect of Measurement-Based Care depression treatment on HIV medication adherence and health outcomes: Rationale and design of the SLAM DUNC Study

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Abstract

Depression affects 20–30% of people living with HIV/AIDS (PLWHA) in the US and predicts greater sexual risk behaviors, lower antiretroviral (ARV) medication adherence, and worse clinical outcomes. Yet little experimental evidence addresses the critical clinical question of whether depression treatment improves ARV adherence and clinical outcomes in PLWHA with depression. The Strategies to Link Antidepressant and Antiretroviral Management at Duke, UAB, and UNC (SLAM DUNC) Study is a randomized clinical effectiveness trial funded by the National Institute for Mental Health. The objective of SLAM DUNC is to test whether a depression treatment program integrated into routine HIV clinical care affects ARV adherence. PLWHA with depression (n=390) are randomized to enhanced usual care or a depression treatment model called Measurement-Based Care (MBC). MBC deploys a clinically supervised Depression Care Manager (DCM) to provide evidence-based antidepressant treatment recommendations to a non-psychiatric prescribing provider, guided by systematic and ongoing measures of depressive symptoms and

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side effects. MBC has limited time requirements and the DCM role can be effectively filled by a range of personnel given appropriate training and supervision, enhancing replicability. In SLAM DUNC, MBC is integrated into HIV care to support HIV providers in antidepressant prescription and management. The primary endpoint is ARV adherence measured by unannounced telephone-based pill counts at 6 months with follow-up to 12 months and secondary endpoints including viral load, health care utilization, and depressive severity. Important outcomes of this study will be evidence of the effectiveness of MBC in treating depression in PLWHA and improving HIV-related outcomes.

Keywords

HIV; depression; adherence; Measurement-Based Care; randomized controlled trial; effectiveness trial

Introduction

Depression is a serious comorbidity in the clinical management of HIV infection, affecting 20–30% of people living with HIV/AIDS (PLWHA) in the United States. In HIV-infected patients, depression predicts greater sexual risk behaviors, lower antiretroviral (ARV) medication adherence, and worse clinical outcomes. Yet little evidence, especially experimental evidence, addresses the critical clinical question of whether depression *treatment* will *improve* ARV adherence and clinical outcomes in HIV-infected patients with depression. In this paper we present the rationale and design of the Strategies to Link Antidepressant and Antiretroviral Management at Duke, UAB, and UNC (SLAM DUNC) Study, a NIMH-funded randomized clinical effectiveness trial that tests whether a depression treatment program integrated into routine HIV clinical care affects ARV adherence.

Background and Rationale (Summary in Box 1)

Box 1

Background and Rationale: Major points

- Depression is prevalent in HIV patients, and frequently goes clinically unrecognized and untreated.
- Depression is associated with worse ARV adherence and clinical outcomes.
- Standard depression treatments work well for HIV patients.
- In observational studies, depression treatment is associated with better ARV adherence.
- Depression treatment has shown promise in improving medical outcomes in patients with diabetes and hypertension.
- Measurement-Based Care is a feasible model for integrating vigorous antidepressant prescription support into non-psychiatric clinical settings.

Prevalence of depression in HIV patients

Since the emergence of AIDS in the early 1980's, psychiatric needs of PLWHA have been recognized as unique and significant.[1–3] The HIV/AIDS Costs and Services Utilization Study (HCSUS), a U.S. survey of a national probability sample of PLWHA in care, found

that nearly half (48%) of participants had a probable diagnosis of a mental disorder and 35% screened positive for depression.[4] The most common psychiatric diagnoses among PLWHA are mood and anxiety disorders, particularly major depression and other depressive disorders.[5–8] The major mood and anxiety disorders are five to ten times more prevalent in PLWHA than in the general U.S. population.[9] A meta-analysis of studies between 1988 and 1998 found that major depressive disorder was twice as frequent in PLWHA relative to comparable HIV-uninfected persons.[10] More recent evidence continues to bear out this relationship.[11–18] Despite its high prevalence, depression is under-recognized by primary HIV medical providers with subsequent under-utilization of psychiatric treatment.[19]

Association of depression with ARV adherence and HIV clinical outcomes

In PLWHA, depression has been consistently associated with deleterious HIV-related behaviors, particularly poor antiretroviral medication adherence.[20,21] Indeed, a recent meta-analysis of 95 studies encompassing 35,029 participants reported a pooled correlation coefficient across studies for the relationship of depression with medication adherence of r = 0·19 (95% CI: 0·14–0·25), a relationship which was consistent between cross-sectional and longitudinal studies and low-resource and high-resource settings.[22] Adherence is a critical consideration in HIV care where complex ARV regimens play a central role in suppressing viral replication and protecting the immune system.[23] Depression has also been associated with a wide range of unfavorable health outcomes including poorer physical health,[24] decreased quality of life,[25] lower likelihood of receiving ARV medications,[26] poor response to ARV,[27] and increased AIDS-related mortality,[28] as recently summarized in a comprehensive review.[29] In the HIV Epidemiology Research Study (HERS), a multisite longitudinal cohort study of HIV-infected women, participants who were chronically depressed over the course of the study progressed to death from AIDS twice as quickly as participants with intermittent or no symptoms of depression.[28]

Efficacy of standard depression interventions for HIV patients

Standard pharmacological and psychotherapeutic interventions are efficacious in treating depression in PLWHA. Two meta-analyses of randomized controlled trials (RCTs) of antidepressant-based[30] and group therapy-based[31] depression treatment in PLWHA estimated pooled effect sizes of 0.57 (95% CI 0.28–0.85) and 0.38 (0.23–0.53), respectively. Of note, none of the 15 RCTs reviewed in these two meta-analyses considered ARV medication adherence or HIV clinical indicators as secondary outcomes.

Association of depression treatment with improved ARV adherence

The available evidence addressing whether depression treatment improves adherence is limited but promising. A few trials of psychotherapy-based depression treatment strategies in small samples have shown improvements in ARV adherence.[32–34] For example, Weber et al. reported 70% of intervention arm participants achieving at least 95% ARV adherence compared to 50% of treatment-as-usual participants, and Safren reported a Cohen's effect size of 1.0 fpr the difference in continuously measured pre- and post-treatment ARV adherence comparing the CBT arm to the waitlist control arm. Observational evidence has identified an association between antidepressant treatment and improved adherence. Three recent observational studies each analyzed retrospective records and reported higher ARV refill adherence associated with antidepressant prescription and with antidepressant refill adherence.[35–37] For example, among HIV patients with depression, Walkup reported an odds ratio for current-month ARV prescription adherence of 1.28 comparing those with past-month antidepressant prescription to those without, and Yun reported an odds ratio for achieving at least 95% ARV refill adherence of 2.45 comparing those with antidepressant refill adherence above the median to those below the median. More recently, a sophisticated analytic approach indicated higher odds of ARV uptake and adherence as well as virologic

suppression associated with antidepressant treatment in a longitudinal cohort.[38] This work supports earlier observational reports showing an association between appropriate psychiatric treatment, improved ARV adherence, and improved HIV clinical outcomes relative to patients with untreated mental illness.[39,40]

Experimental evidence on whether depression treatment improves clinical outcomes for other chronic diseases

Several randomized controlled trials have been conducted to determine whether chronic medical condition outcomes in patients with comorbid depression can be improved by collaborative care models that integrate treatment for depression and the medical condition. An RCT in patients with diabetes and depression[41] reported improvements in depression but no difference in the primary biomarker of diabetes control (HbA1c). A comparable collaborative care model for hypertensive patients[42] showed significantly improved antihypertensive medication adherence as well as improved blood pressure in the group randomized to the collaborative care intervention compared to the group randomized to usual care. A larger RCT that enrolled patients with either poorly managed hypertension or diabetes and comorbid depression, and proactively followed patients to provide support for medication adherence, demonstrated improvements in a single combined endpoint of hemoglobin A1c, cholesterol, systolic blood pressure, and depression scores in the collaborative care arm relative to usual care.[43] An RCT published in 2011 (after the start of the current study) of a collaborative care model for HIV patients with depression in Veterans Affairs (VA) treatment centers found significant reductions in HIV symptom severity but did not find significant improvements in ARV adherence, using a self-reported measure of ARV adherence and an adherence threshold of 95%.[44] Of note, adherence in this study was measured via self-report, and mean ARV adherence at baseline was relatively high (>90% in both arms), potentially imposing a ceiling effect. This is the first published study the authors are aware of that used a randomized design to test whether a collaborative depression and HIV treatment model could improve ARV adherence. Whether different results would be observed in non-VA patient populations, in populations with lower baseline adherence, or using an objective measure of adherence remains undetermined.

Feasible model for integrating vigorous antidepressant prescription support into non-psychiatric clinical settings

While improving the identification and management of depressive illness in PLWHA in HIV clinics has promise to improve both HIV and depression outcomes, depression treatment strategies need to be effective and sustainable in busy, real-world clinic settings. The large-scale adaptation of psychotherapeutic interventions into HIV clinical care remains challenging because of staffing requirements, resource constraints, and limited available mental health treatment. Interventions that equip existing clinic staff with simple tools to effectively prescribe and monitor antidepressant treatment may be implemented more readily and scaled up more quickly into widespread practice.

A feasible depression intervention referred to as Measurement-Based Care (MBC) has been successfully implemented in primary care medical settings for patients with comorbid medical conditions.[45,46] The MBC approach is based upon use of a clinically supervised care manager to provide evidence-based antidepressant treatment recommendations to a non-psychiatric prescribing provider, with care guided by systematic and ongoing measures of depressive symptoms and side effects. Such a model allows care of the depressed HIV patient to remain in the HIV clinic “medical home.” The foundation for MBC was developed in the Texas Medication Algorithm Project (TMAP) in 1996[47] and was further refined and extended for use in primary care medical settings in the design and implementation of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

study, the largest prospective trial of depression treatment ever conducted.[48,49] Using MBC, STAR*D achieved equivalent rates of depression remission in both psychiatric and primary care settings, demonstrating the strategy's potential to deliver high-quality depression management in non-psychiatric settings.[46]

Summary

Depression is prevalent in PLWHA. Observational data support an association between depression and poor ARV adherence and HIV clinical outcomes. Standard depression treatment approaches are efficacious in HIV-infected patients, and observational evidence supports an association between depression treatment and improved ARV adherence. A handful of small RCTs have tended to show improved ARV adherence among PLWHA randomized to psychotherapy-based mental health treatment interventions. Interventions focused on antidepressant treatment integrated into the HIV medical home, such as the MBC model proposed in this project, will more likely be able to address the resource constraints and lack of psychiatric treatment expertise that defines most HIV clinical settings and the lack of access to mental health services that is the norm for most of the increasingly poor, uninsured, and disenfranchised HIV population in the US. Antidepressant-based treatment approaches have shown promise in improving medical outcomes for patients with hypertension and diabetes, but at the time this study was designed, no similar studies had been reported for HIV patients with depression.

Purpose

To address this gap in the literature, we designed and are implementing the SLAM DUNC Study to test whether, relative to enhanced usual care, vigorous antidepressant management supplemented with brief adherence counseling improves HIV medication adherence for patients with HIV and depression. SLAM DUNC, or Strategies to Link Antidepressant and Antiretroviral Management at Duke, UAB, and UNC, is a real-world, effectiveness-oriented, three-site randomized controlled trial. In the intervention arm, antidepressant management is provided by the treating HIV clinician with decision and follow-up support from a Depression Care Manager (DCM), following the Measurement-Based Care (MBC) model described below. In the intervention arm, the DCM also offers three motivational interviewing-based adherence counseling sessions. In the enhanced usual care arm, the HIV clinician receives the results of the participant's baseline psychiatric evaluation and is free to provide depression care or refer to another clinician for treatment, but does not receive decision and follow-up support from the DCM.

Funding and registry

SLAM DUNC is a five-year study funded in 2009 by the National Institute of Mental Health and the National Institute of Nursing Research (R01-MH086362) and is registered in ClinicalTrials.gov (NCT01372605).

Design

SLAM DUNC is a three-site randomized controlled effectiveness trial. The implementation sites are the infectious diseases clinics at three academic medical centers: Duke University (lead site; Clinic 2J), the University of North Carolina at Chapel Hill (UNC Infectious Diseases Clinic), and the University of Alabama at Birmingham (1917 Clinic).

The study design is based on a conceptual model that posits that HIV-infected patients with depression will show improved ARV adherence following depression treatment and a reduction in depressive severity. The reduction in depressive severity will in turn improve

HIV medical care-related self-efficacy and coping behaviors (mediators; see Figure 1). Adherence counseling will improve self-efficacy and coping, thereby improving adherence, but without affecting depressive severity. The model posits that potential moderators of intervention effectiveness include baseline depressive severity and comorbid substance abuse and anxiety disorders, specifically, that higher baseline depressive severity and comorbid disorders may be associated with reduced effectiveness.

Inclusion and exclusion criteria

Patients seeking HIV care at participating sites are eligible if they are HIV-positive, ages 18–65 years old, English-speaking, are currently prescribed any FDA-approved antiretroviral medication or expect to start ART within the next month, have a total score of 10 or higher on the Patient Health Questionnaire-9, and are subsequently confirmed to have a current major depressive episode on the Mini International Neuropsychiatric Interview (MINI).[50] Both new and established patients are eligible for enrollment. Patients are excluded if they have a history of or current bipolar or psychotic disorder, have failed adequate trials of two or more different antidepressants in the current major depressive episode, have current substance dependence requiring inpatient hospitalization, demonstrate acute suicidality or other psychiatric presentation requiring immediate hospitalization, or are not mentally competent. Age range and psychiatric comorbidity exclusion criteria reflect the fact that different depression treatment approaches are indicated for adolescents, those over 65, or for depressive symptoms presenting as part of a bipolar or psychotic disorder. Patients with treatment-resistant depression are unlikely to respond to the antidepressant management strategy used in this study, so patients are excluded who have failed adequate trials of two or more FDA-approved antidepressant medications in the current major depressive episode. For the purposes of this study, to be considered an adequate trial of an antidepressant, the patient must have been taking a moderate to high dose (generally, at least half the maximum FDA-approved dose) for at least six weeks. Patients are not excluded if they are on an antidepressant at enrollment, as long as they do not meet the threshold of having failed two or more adequate antidepressant trials. Patients are not excluded if they are involved in other substance use or mental health counseling treatment.

Pregnancy

Pregnant women are not categorically excluded from the study, given the greater potential benefits to mother and child of improved adherence and mental health and the relatively safe profile of antidepressants in pregnancy and postpartum.[51–53] The American College of Obstetrics and Gynecology currently recommends that treatment with SSRIs or selective norepinephrine reuptake inhibitors (SNRIs) during pregnancy should be individualized.[54] The HIV provider and patient make joint decisions about testing for pregnancy and antidepressant prescription for pregnant or breastfeeding women as part of usual clinical care in both conditions. The research study does not provide pregnancy testing but encourages female participants, if they know or suspect they may be pregnant, to discuss the issue with their provider as part treatment planning. The provider will help them weigh potential neonatal effects against the benefits to both mother and child of successfully treating a major depressive disorder.

Enrollment

After provision of informed consent, psychiatric inclusion and exclusion criteria are assessed with the Mini International Neuropsychiatric Interview (MINI).[50] After confirmation of eligibility, baseline research data collection is completed by a blinded study team member. Upon completion of baseline data collection, the participant is randomized.

Study Conditions

In the intervention condition, patients receive ongoing depression monitoring and HIV providers receive initial and ongoing antidepressant management decision support from the Depression Care Manager (DCM) following the Measurement-Based Care (MBC) model, described in more detail below. In brief, MBC is designed to equip clinically supervised non-psychiatric providers (DCMs) to work with prescribing providers to provide vigorous antidepressant management and achieve maximal depression response. The DCM performs frequent, standardized monitoring of side effects and depressive symptoms, and uses an algorithm to provide decision support that focuses on responding promptly to distressing side effects and increasing doses as needed to achieve full depression remission. In the intervention condition, patients additionally receive three motivational interviewing-based counseling sessions focused on antiretroviral medication adherence, adapted from an adherence intervention (PACT).[55]

In the enhanced usual care arm, HIV providers receive the results of the initial psychiatric assessment (e.g., confirmation of diagnosis of an episode of major depressive disorder) but do not receive further decision support or patient follow-up from the DCM. The HIV provider is free to implement any depression treatment plan he or she wishes, including initiating an antidepressant or referring to other resources. A paper version of the decision algorithm guiding the intervention arm is available in the common workspace of all clinics and is accessible to providers of patients in the enhanced usual care arm.

Outcomes

The study's primary outcome is a comparison between the arms of ARV adherence at 6 months, measured by unannounced phone-based pill count.[56] Secondary outcomes include antiretroviral medication adherence at 12 months; viral load at 6 and 12 months; depressive symptomatology at 6 and 12 months, measured by the Hamilton Rating Scale for Depression; HIV medical appointment adherence over 12 months; and cost-effectiveness, measured by changes in cost of prescriptions and health care utilization relative to the cost of the intervention.

Schedule of events

Figure 2 describes the flow of study activities, and Figure 3 summarizes the schedule of research and clinical activities from a participant's perspective.

Design choices and consideration of strengths and limitations

SLAM DUNC is designed as an effectiveness trial, with the primary goal of measuring the impact of real-world implementation of vigorous antidepressant management on HIV medication adherence. This principle led to several design choices which distinguish the design from an efficacy study design:

1. The study does not provide or pay for recommended antidepressant medications. Barriers or delays in accessing antidepressant medications are systematically measured.
2. The study does not require that providers follow the Depression Care Manager's antidepressant dosing recommendations. Reasons for provider divergence from recommendations are systematically measured.
3. The study's inclusion criteria are as broad as possible. Specifically, participation is not restricted to patients with depression alone, but is open to patients with comorbid substance abuse and anxiety disorders (including those receiving

substance abuse treatment), in recognition of the fact that the majority of HIV patient with depression have at least one other Axis I disorder as well.[57]

We decided to focus this study on estimating the impact of MBC as a clinic-wide intervention. This design choice led to three key decisions:

1. Since MBC in a real-world context would likely be offered to all depressed patients, not just to those with low HIV medication adherence, we decided to enroll all patients with depression regardless of initial HIV medication adherence.
2. Since our goal was to estimate the "value added" of MBC relative to current depression management practice, and since it would be unethical to prohibit depressed patients from receiving depression treatment, we did not set any bounds around the treatment plans that providers and patients could pursue in the enhanced usual care arm.
3. As the question of interest was to estimate the effect of the presence vs. absence of MBC, we selected a usual care comparison arm rather than an attention-matched comparison arm, since the latter would not represent the state of care in the absence of MBC.

Much discussion at the design stage focused on blinding and its impact on the comparison condition. The nature of the intervention makes blinding unfeasible for participants, providers, and study interventionists (although research outcome assessors are blinded to study condition). The absence of blinding raises the question of whether participants' knowledge of treatment assignment could bias results. It is important to note that this study is not a trial of a specific medication, but of a care coordination strategy, and that participants in both arms are in fact eligible to receive antidepressants or other depression treatment. The key element that differs between the arms is whether or not the Depression Care Manager collaborates with the HIV provider in developing a treatment plan and providing follow-up. In order to avoid giving participants the impression that one arm is denied treatment, the consent form states that in one arm, the Depression Care Manager will work with the HIV provider to develop a depression treatment plan, while in the other arm, the HIV provider will develop a depression treatment plan on his or her own.

Intervention condition: Measurement-Based Care and motivational interviewing-based adherence counseling

Overview of MBC

Measurement-Based Care (MBC) is a state-of-the-art depression care management strategy that trains clinic support personnel as Depression Care Managers (DCMs) who assist non-psychiatric clinicians in providing guideline-concordant, vigorous antidepressant treatment. Functioning as decision support for the clinicians, these DCMs perform initial assessments, monitor symptoms and side effects, and make dosing recommendations to the treating clinician (here, the HIV medical provider). DCMs guide providers in choosing from a list of antidepressants that have been assessed for efficacy, tolerability, and interaction with ARV medications.

DCMs receive initial training in the MBC algorithm and antidepressant dosing, side effects, and interactions with antiretroviral medications. A psychiatric professional provides weekly clinical supervision and as-needed support to the DCM to ensure quality of care and provide ongoing training.

MBC measures

In the SLAM DUNC Study, depressive symptom severity is assessed with the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 score can range from 0–27, with 0–4 indicating no depression, 5–9 indicating mild depressive symptoms, 10–19 indicating moderate depressive symptoms, and 20–27 indicating severe depressive symptoms. A score of 10 or above is normally used as a cutoff indicating likely major depression, including in HIV patients.[58] Antidepressant side effect burden is assessed with the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER).[59]

Schedule of events

At baseline, the DCM measures depressive severity. If the patient is currently on an antidepressant, the DCM also measures the baseline antidepressant side effect burden. The DCM then recommends a treatment plan to the HIV clinician.

Critical Decision Points (CDP) for possible antidepressant medication changes occur every 4 weeks. At these visits, the DCM re-assesses depressive symptoms and side effects. Based on the depressive symptoms and side effects, the DCM makes a new treatment recommendation to the HIV clinician guided by the decision algorithm. In general, if the side effects are intolerable, the recommendation is to address the side effects if possible, reduce the dose of the antidepressant, or switch to a new antidepressant. If side effects are absent or tolerable, the recommendation is generally to maintain the dose if the patient has achieved remission or increase the dose if remission has not been achieved.

The DCM has interim contacts with the patient every two weeks between Critical Decision Points. These are brief contacts to assess side effects. Generally no treatment change recommendation arises from these contacts unless distressing side effects are noted.

At CDP 3 (after 12 weeks on a given antidepressant regimen), if the patient has achieved remission, the recommendation is to continue on the same dose and enter a maintenance phase of treatment, during which the patient and DCM have contact every 2–3 months to confirm continued remission. If the patient has not achieved remission, the recommendation is generally to declare the treatment a failure and recommend augmentation with a second antidepressant or switch to a new antidepressant. After two failed trials the recommendation is to refer for a psychiatric consultation.

The treatment team

Treatment decisions are the result of collaboration between the patient, HIV clinician, DCM, and supervising psychiatrist (Figure 3). The depression care manager completes standardized assessments with the patient and follows the MBC algorithm to provide recommendations to the HIV clinician as described above. The HIV clinician and patient make final treatment decisions with decision support from the DCM. The supervising psychiatrist reviews all encounters, recommendations, and treatment plans with the DCM on a weekly basis to provide quality assurance and ongoing training, monitor adherence to the MBC algorithm, and offer any supplemental recommendations. This weekly supervision is facilitated by a web-based patient tracking system in which key data for each encounter (depressive severity, side effects, algorithm recommendation, treatment plan, psychiatrist's review) are organized for easy review. The supervising psychiatrist is also available to the DCM and HIV clinician for consultations about individual patients as needed.

Adherence counseling

Intervention arm participants have three counseling sessions with the DCM focused on antiretroviral medication adherence, based on a theoretically grounded, Motivational

Interviewing approach manualized in the Participating And Communicating Together (PACT) intervention.[55,60] Motivational interviewing is a client-centered, goal-directed counseling style originally developed to treat substance abuse and later adapted to facilitate a broader spectrum of health behavior changes.[61–63] Motivational interviewing does not follow an invariant structure but includes five counseling techniques aimed at helping clients resolve ambivalence about a health behavior: (1) expressing empathy; (2) developing discrepancy; (3) avoiding argument; (4) rolling with resistance; and (5) supporting self-efficacy.[61] Motivational interviewing is based on the premise that a patient's readiness for behavior change is not a fixed characteristic of the person, but a fluctuating factor that can be altered as a result of an interaction with a counselor.[64] In SLAM DUNC, participants have three one-hour sessions (one in-person and two by phone) over three months. DCMs capture the content of these sessions on standardized data recording sheets and have regular supervision with a Motivational Interviewing supervisor to ensure fidelity.

Research Procedures

Unannounced phone-based pill counts

The primary outcome measure of ARV adherence is measured through unannounced phone-based pill counts. Unannounced home-based pill counts were established as an objective and valid measure of ARV adherence by Bangsberg and colleagues,[65] and the methodology was adapted for phone implementation and validated by Kalichman and colleagues.[56] A research assessor blinded to study arm contacts each participant at approximately 30-day intervals for 12 months to count the participant's current antiretrovirals and to gather information on pills dispensed, pills discarded, and other gains and losses since the last pill count. The study provides cell phones when needed to assist in reaching participants.

Research interviews

Information on additional outcomes (depressive severity, health care utilization, sexual risk behaviors), covariates (sociodemographics), and potential mediators and moderators of intervention effects (self-efficacy, coping behaviors, comorbid mental health diagnoses) are captured during research interviews conducted every three months by a research assessor blinded to study arm.

Sample size and power

In determining sample size requirements, the study team focused on the definition of a minimum clinically significant difference in the primary outcome, continuously measured ART adherence. The team defined this difference as a change of ≥10 percentage points; a study result showing a change <10 percentage points was believed to be unlikely to substantially influence policy or practice. Based on standard deviation estimates published in similar studies,[34] a 5% Type I error probability, two-tailed tests, and 80% retention at the primary endpoint, the target sample was calculated to have 80–90% power to detect a difference of ≥10 percentage points.

Monitoring of serious adverse events

The occurrence of serious adverse events is assessed, reported, and monitored systematically and carefully. The serious adverse event of primary concern in this population is suicide. Suicidal ideation is probed at baseline for all participants, at every quarterly research interview for all participants, and at every MBC contact for intervention participants. It was expected that the prevalence of any level of suicidal ideation would be high: approximately 50% of patients with depression in medical or psychiatric settings endorse some level of suicidal ideation.[66,67] In SLAM DUNC, if suicidal ideation is reported, it is classified by the

assessor as either passive (thoughts of death without a specific plan of self-harm), active not requiring immediate intervention (a specific plan of self-harm without immediate intent), or active requiring immediate intervention (a specific plan of self-harm with immediate intent). When a participant reports active suicidal ideation that requires immediate intervention, the study staff member speaking with the patient immediately contacts a clinician, if in clinic by following the clinic's suicidality response protocol, or if not in clinic by paging a study psychiatrist. All reports of suicidal ideation are logged either on the clinical supervision website (MBC encounters) or through an SAE reporting system (research interviews) and are reviewed by a study psychiatrist. Other SAEs (hospitalizations, emergency department visits) are logged in similar fashion. Overall frequency of suicidal ideation and other SAEs in the study population is reviewed quarterly by the entire investigative team to assess whether prevalence is exceeding expectations. An independent Data Safety and Monitoring Board reviews SAEs annually.

Human Subjects Protection and Ethical Approvals

This protocol has been approved by the Duke University Medical Center Institutional Review Board (IRB) (#Pro00019233), the University of North Carolina at Chapel Hill Biomedical IRB (#09-1882), and the University of Alabama at Birmingham IRB (#F110202004). Human subjects protection issues of particular consideration during the approval process included careful monitoring of suicidal ideation as well as procedures for situations in which a concern of an imminent threat of harm to or by the participant might require a breach to confidentiality.

Current status

SLAM DUNC began enrollment in April 2010 with target enrollment of 390. As of December 2011, 153 participants had been enrolled and randomized. Enrollment is projected to continue through April 2013 with follow-up through April 2014.

Conclusion

SLAM DUNC uses a randomized clinical effectiveness trial design to test whether a depression treatment model integrated into routine HIV clinical care affects ARV adherence and improves HIV clinical outcomes relative to a usual care control. Key components of the intervention include use of depression care managers (DCMs) to provide treatment recommendations guided by an evidence-based Measurement-Based Care algorithm; weekly supervision of DCMs through a review of enrolled patients by a psychiatric care team; delivery of recommendations to the HIV clinicians by the DCMs; monthly patient visits at critical decision points to assess the need for a modification of the antidepressant management plan; and vigorous dose escalation during the acute phase of antidepressant treatment. Key components of the study design include estimation of effectiveness in real-world settings, the use of unannounced phone-based pill counts as the measure of the primary outcome variable, ARV adherence, and a primary focus on the effect of depression treatment on HIV-related outcomes including ARV adherence.

A strength of this study is the use of an algorithm and model–Measurement-Based Care–that has been successfully applied in multiple busy medical clinic settings to improve depression outcomes in patients with comorbid medical illnesses. Since the DCM role can be effectively filled by a behavioral health provider, nurse, or care manager given appropriate training and supervision, and the intervention has limited time requirements, this model is potentially replicable in a wide range of resource-constrained treatment settings for HIV or other chronic medical illnesses. Given the high prevalence of depression in HIV patients and the increasing push to coordinate multiple medical services in one "medical home,"[68] the

model deployed in this study is likely to be applicable for a substantial proportion of HIV patients, especially in settings with limited access to specialized mental health services. Important outcomes of this study will be evidence of the effectiveness of MBC in treating depression in PLWHA, evidence of the effectiveness of MBC in improving HIV-related outcomes, a detailed analysis of process measures contributing to or hindering its implementation in our sites, and a treatment manual to facilitate replication.

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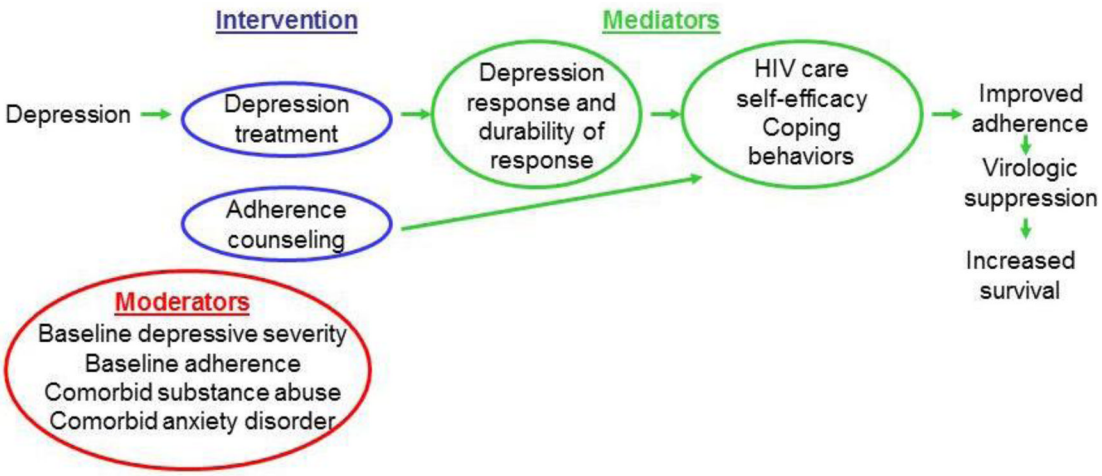

Figure 1.
Conceptual model.

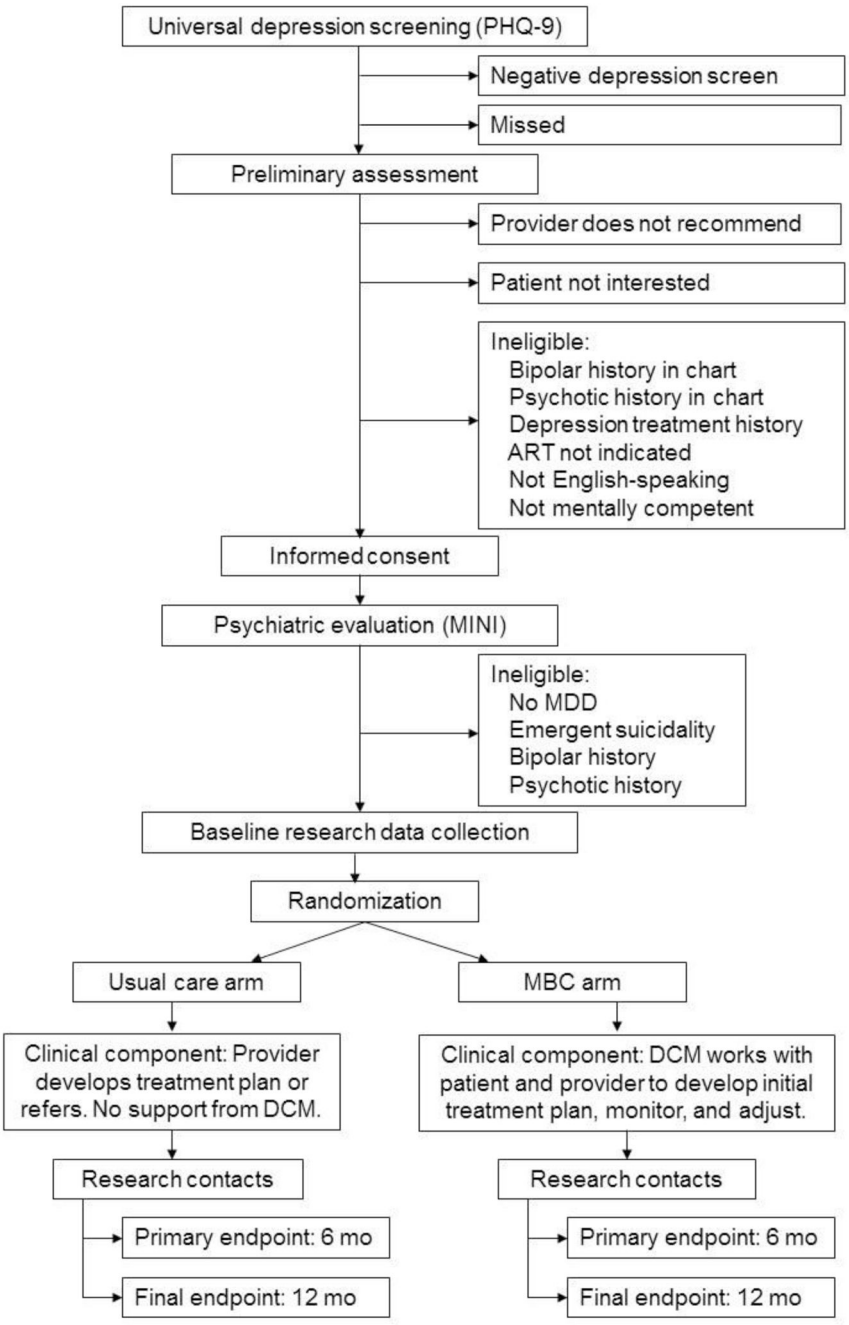

Figure 2.
Flowchart of study activities.

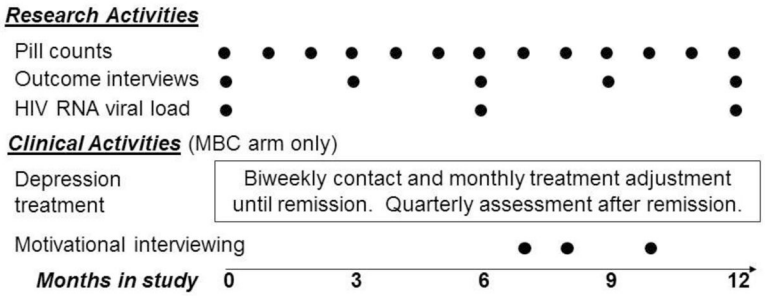

Figure 3.
Schedule of study activities from a participant's perspective.

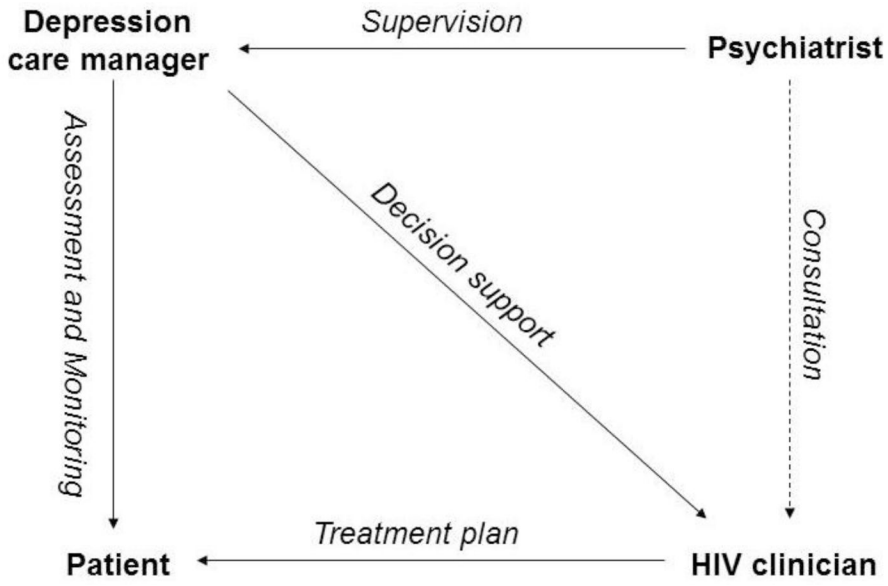

Figure 4.

Communication flow in Measurement-Based Care treatment team.

DCM conducts standardized assessment & monitoring of patient's depression. DCM provides decision support to HIV clinician about depression treatment plan. HIV clinician decides on treatment plan with patient. Psychiatrist provides weekly and as-needed supervision to DCM. Psychiatrist available for consultation on complicated cases.

Table 1

Schedule of Research Outcomes Data Collection

Domain	Baseline	3 months	6 months	9 months	12 months	Monthly (Months 0–12)
Sociodemographics	•					
Mood and anxiety disorder diagnoses (MINI)	•					
Depressive symptoms (HAM-D)	•	•	•	•	•	
Alcohol and drug abuse and dependence diagnoses (MINI)	•		•		•	
General health (SF-12)	•		•		•	
Fatigue (HRFS)	•		•		•	
HIV-related symptoms	•	•	•	•	•	
Self-reported ARV adherence	•	•	•	•	•	
HIV-related self-efficacy	•	•	•	•	•	
Coping styles	•	•	•	•	•	
Sexual risk behaviors	•	•	•	•	•	
Health care utilization	•	•	•	•	•	
HIV-related identity (PIQ)	•				•	
ARV adherence: Phone-based pill counts						•
Recent stressful life events						•

MINI: Mini International Neuropsychiatric Interview. SF-12: Short-Form 12. HRFS: HIV-Related Fatigue Scale. PIQ: Perceived Identity Questionnaire.